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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: RONALD J. PETTIS, et al.	Confirmation No.: 7814
Serial No.: 09/606,909	Art Unit: 3763
Filed: June 29, 2000	Examiner: Michael J. Hayes
For: INTRADERMAL DELIVERY OF SUBSTANCES	Attorney Docket No.: 11219-008-999 (P-4901)

THIRD DECLARATION OF DR. RONALD J. PETTIS
UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, DR. RONALD J. PETTIS, do hereby declare and state:

1. I am a co-inventor of the subject matter disclosed and claimed in the above-identified patent application (herein referred to as "the '909 application").

2. I am currently Technology Manager, at Becton, Dickinson and Company, Inc. which is the assignee of the '909 application.

3. My academic background, technical experience and list of publications are set forth in my *curriculum vitae*, attached hereto as Exhibit A.

4. I have reviewed the claims of the '909 application as amended in the concurrently filed Amendment under 37 C.F.R. § 1.111. I have also reviewed U.S. Patent No. 5,848,991 to Gross *et al.* (herein referred to as "Gross").

5. The presently claimed invention of the '909 application relates to a method for delivering insulin to a specific depth of a human subject's skin through a hollow needle

having an outlet depth and exposed height which are located within the intradermal compartment. The claimed method specifies placement of a needle within the subject's skin so that neither the needle's outlet depth nor its exposed height are outside the intradermal compartment. By using the claimed method, a person of ordinary skill in the art achieves control of the resulting pharmacokinetic profile through intradermal administration of insulin. In contrast, placement of the needle outlet's depth and exposed height outside the intradermal compartment will not result in the instantly claimed higher maximum plasma concentration and higher bioavailability of insulin. Placement of the outlet's depth and exposed height above the intradermal compartment would result in leakage of the injected insulin up and out of the injection site; while placement of the outlet's depth and exposed height below the intradermal compartment would result in delivery to the subcutaneous compartment.

6. The intradermal delivery method claimed in the '909 application is distinct from Gross's purported intradermal delivery method. A careful reading of Gross indicates that while there might be some overlap in terms of needle length with the '909 application (*see*, Gross at col. 4, lines 10-13), the reference as a whole fails to teach how to specifically deliver a substance into the intradermal compartment in order to achieve the improved pharmacokinetic parameters as claimed in the '909 application. Critical features of the invention of the '909 application are simply absent from Gross. Unlike Gross, the '909 application teaches the importance of not only the needle length but also proper positioning of the needle outlet's exposed height into the intradermal compartment of the subject's skin. There is absolutely no disclosure in Gross concerning the height and depth of the needle outlet or the criticality of its placement within the intradermal compartment. Gross does not describe insertion of a needle so that both the depth and exposed height of its outlet (*i.e.*, orifice) are located within the intradermal compartment of the subject's skin. This feature, however, is a requirement specified in Claim 29 of the '909 application. Nor does Gross

disclose the use of intradermal administration as a means of controlling drug pharmacokinetics; further, Gross fails to differentiate intradermal administration from subcutaneous administration.

7. In addition to its effect on insulin's pharmacokinetic profile, further evidence of the significance of accurately placing the needle outlet's depth and exposed height in the intradermal compartment is shown by the outcome of pharmacodynamic studies conducted with insulin. Studies describing the pharmacodynamic response upon administration of insulin to animals in accordance with the claimed invention are described below in paragraphs 8-15.

8. I describe below the results of time course studies of blood glucose concentrations in rabbits upon administration of insulin in accordance with the claimed invention. I designed the studies described herein, which were conducted under my direction, and I am familiar with the results. The studies demonstrate that when insulin is administered in accordance with the claimed method at the same concentration (100 IU/mL) and at the same rate (0.1 mL/h) as described in Exhibit 1 of Gross (see, col. 10, lines 32-45), a very different pharmacodynamic result is achieved. The different result could only result from a different method of delivery. In fact, as a result of intradermal administration of insulin in accordance via the claimed method at 100 IU/mL, the blood glucose concentrations of the test animals dropped to levels which could not be reversed by ceasing administration of insulin, nor by intervening through administration of glucose to the hypoglycemic test animals. If Gross had been practicing intradermal delivery as claimed in the '909 application, the same result would have been observed; it was not.

9. We administered two different insulin types in the studies. In one study, designated Study 1, we administered to rabbits regular human insulin (Lilly Humulin®). In the other study, designated Study 2, we administered to rabbits a fast acting human insulin

analog (Lilly Lispro®) reported to have a faster onset of, and shorter duration of action than human insulin.

10. We administered a 100 IU/mL solution of insulin at a rate of 0.1 mL/h for two hours. We injected insulin in accordance with the invention at three different depths; at 1 mm, at 2 mm, and at 3 mm. These depths span the range of 0.5-3.0 mm for the penetration depths described at p. 4, lines 5-6 of the '909 application.

11. We injected the rabbits on the right/dorsal flank region using Becton Dickinson single needle catheter sets having a 34 gauge needle. We used a Harvard Apparatus PHD 2000 Program Pump having qualified accuracy for both volume and rate of delivery.

12. In order to further confirm that insulin administered by the method described in paragraphs 10-11 above was injected in the intradermal compartment, in Study 1, we also assessed blood glucose concentrations in a rabbit in which insulin was delivered beneath the surface of the skin into the intradermal compartment using a narrow gauge needle of 1.5 mm length inserted at a shallow angle to the skin to further reduce the depth of administration. We also determined blood glucose concentrations in a rabbit which was not administered with insulin as a negative control in Study 1.

13. For each rabbit in both studies, we analyzed the blood glucose concentrations from blood samples withdrawn from the ear vein using a 25 gauge needle. We sampled the rabbits at 0, 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, and 240 minutes. We determined blood glucose concentrations on two different Accuchek Glucose Meters, and averaged the results for each time point.

14. Results - Exhibits B and C present the results of Study 1 (using human insulin), and Exhibits D and E present the results of Study 2 (using the human insulin analog). Exhibits B and D show the average blood glucose levels in mmol/L over the time

course of the studies. Exhibits C and E show the results of the studies, wherein the blood glucose concentrations are normalized to the starting time (time=0) concentration for each rabbit, and thus, present the results obtained for each time point as a percentage of the starting blood glucose concentration.[1] For comparative purposes, the graphs in Exhibits B, C, D, and E superimpose the data reported directly from Figure 12 of Gross.

15. Results - All rabbits receiving insulin in the studies experienced more precipitous drops in blood glucose concentrations and lower maximal glucose concentrations than reported in Gross.[2] These observations held for administration of insulin at all three depths (1 mm, 2 mm, and 3 mm) as well as for insulin administered using the 1.5 mm length in Study 1. In fact, all rabbits receiving insulin in the studies had to be humanely euthanized between 2 and 2.5 hours due to seizures caused by severe hypoglycemia, or due to two consecutive blood glucose concentration readings of $\leq$ 10 mg/dL.[3] The severe hypoglycemia experienced by the rabbits could not be reversed by ceasing administration of insulin, nor by administration of glucose. Administration of either type of insulin, *i.e.*, human insulin (in Study 1) and human insulin analog (in Study 2), in accordance with the claimed invention resulted in more precipitous drops in blood glucose concentrations and lower maximal glucose concentrations than reported in Gross.

16. I declare further that all statements made in this Declaration of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and that like so made are punishable by fine or imprisonment, or both, under

[1] Presentation of the blood glucose concentration as a percentage change from the starting blood glucose concentration, rather than the absolute blood glucose concentration, facilitates comparison of the blood glucose changes across the population of rabbits used in the study.

[2] Based on tissue site biopsies, the average skin thickness of the rabbits used in the studies was 1.5 mm.

[3] Humane euthanasia endpoints occurred per an institutional animal care and use committee.

Section 1001 of Title 19 of the United States code and that such willful false statements may jeopardize the validity of this application and any patent issuing thereon.

Dated: June 15, 2007

RONALD J. PETTIS

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
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NAME	POSITION TITLE
Ronald J. Pettis, Ph.D.	Sr. Scientist; Technology Manager
eRA COMMONS USER NAME	Therapeutic Drug Delivery
	BD Technologies, Research Triangle Park, NC

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Georgia Institute of Technology	B.S. *cum laude*	1986	Chemistry
University of North Carolina at Chapel Hill	M.S	1988	Chemistry
University of North Carolina at Chapel Hill	Ph.D.	1991	Chemistry

Positions and Employment

1991-1994- Research Fellow, School of Pharmacy, University of North Carolina, Chapel Hill, NC
1994-1996 Research Associate, School of Pharmacy, University of North Carolina, Chapel Hill, NC
1996-2001 Scientist, Therapeutic Drug Delivery, BD Technologies, RTP, NC
2001-present Sr. Scientist, Manager, Therapeutic Drug Delivery, BD Technologies, RTP, NC

Honors and Professional Memberships

1990-present Member, American Association of Pharmaceutical Sciences
2003-present Member, Controlled Release Society
2000-present Member, BD Technologies Institutional Animal Care and Use Committee
2001 Wesley J. Howe Award for Technology Innovation, corporate achievement award

Issued Patents

1. United States Patent 6,440,096 August 27, 2002, Microdevice and method of manufacturing a microdevice, AG Lastovich; JD Evans; **RJ Pettis**
2. United States Patent 6,595,947 July 22, 2003, Topical delivery of vaccines; JA Mikszta; JM Brittingham; J Alarcon; **RJ Pettis**; JP Dekker III
3. United States Patent 6,607,513 August 19, 2003, Device for withdrawing or administering a substance and method of manufacturing a device; J. Down; NG Harvey; FE Martin; **RJ Pettis**, AG Lastovich
4. United States Patent 6,656,147 December 2, 2003 Method and delivery device for the transdermal administration of a substance; M Gertsek; BM Wilkinson; **RJ Pettis**
5. United States Patent 6,689,100 February 10, 2004 Microdevice and method of delivering or withdrawing a substance through the skin of an animal; RI Connelly, **RJ Pettis**
6. United States Patent 6,722,364 April 20, 2004 Medicament inhalation delivery devices and methods for using the same; RI Robert; VJ Sullivan; CD Shermer; A Bhuta; **RJ Pettis**
7. United States Patent 6,808,506. October 26, 2004, Device and method for delivering or withdrawing a substance through the skin, AG Lastovich; JK Fentress; J Griggs; **RJ Pettis**; D Sutter; FE Martin; MI Haider
8. United States Patent 6,858,018 February 22, 2005, Iontophoretic devices, PG Green; **RJ Pettis**; MR Brosnan-Cook
9. United States Patent 7,040,316 May 9, 2006, Medicament inhalation delivery devices and methods for using the same; RI Connelly; VJ Sullivan; CD Shermer; A Bhuta; **RJ Pettis**
10. United States Patent 7,060,059 June 13, 2006, System and method for initiating and maintaining continuous, long-term control of a concentration of a substance in a patient using a feedback or model-

based controller coupled to a single-needle or multi-needle intradermal (ID) delivery device, S Keith; RS Parker; NG Harvey; **RJ Pettis**, JD DeNuzzio; G Vonk

11. United States Patent United States Patent 7,083,592, August 1, 2006, Device and method for delivering or withdrawing a substance through skin, AG Lastovich, JK Fentress, J Griggs, **RJ Pettis**, D Sutter, FE Martin, MI Haider,
12. 37 patents pending

Publications

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2. **Pettis RJ**, Hall I, Costa D, Hickey AJ. Aerosol delivery of muramyl dipeptide to rodent lungs. AAPS PharmSci. 2000;2(3):article 25
3. Mikszta JA, Alarcon JB, Brittingham JM, Sutter DE, **Pettis RJ**, Harvey NG. Improved genetic immunization via micromechanical disruption of skin-barrier function and targeted epidermal delivery. Nat Med. 2002 Apr;8(4):415-9.
4. **Pettis RJ**, Knowles MR, Olivier KN, Kazantseva M, Hickey AJ. Ionic interaction of amiloride and uridine 5'-triphosphate in nebulizer solutions. J Pharm. Sci. 2004 Sep;93(9):2399-406.
5. **Pettis RJ**, Microneedle based drug delivery: a promising minimally invasive method for parenteral administration, Drug Delivery Companies Report, Spring/Summer 2004
6. Mikszta J, Haider MI, **Pettis RJ**, Microneedles for Drug and Vaccine Delivery in Skin delivery systems: transdermals, dermatologicals, and cosmetic actives, 1st ed; JJ. Wille ed., 2006
7. Laurent PE, **Pettis RJ**, Easterbrook W, Berube J, Evaluating New Hypodermic and Intradermal injection Devices, Med. Dev. Technology Mar; 17 (2), 2006

Abstracts

1. **Pettis, RJ**, Middleton, BA, Cho, MJ (1994) Preformulation studies of UCN-01: Solubility and stability enhancement by polyvinylpyrrolidone binding, Pharm. Res., 11:S230.
2. **Pettis, RJ**, Becton, BA, Cho, MJ, Tabibi, E (1995) Preformulation studies of sarcosine-chloroethylnitrosourea (SarCNU), Proc. Am. Assoc. Canc. Res., 36:311.
3. Atkins, KM, Lalor, CL, Concessio, NM, **Pettis, RJ**, Hickey, AJ (1995) Aerodynamic size characterization, lung deposition and alveolar macrophage uptake of microparticulate suspension aerosols in guinea pigs, abstract, 17th Annual Undergraduate Research Seminar, West Virginia University.
4. Lalor, CJ, Atkins, KM, Concessio, NM, **Pettis, RJ**, Hickey, AJ (1996) Lung deposition and alveolar macrophage uptake of microparticulates from suspension aerosols in guinea pigs, abstract, Society of Toxicology 35th Annual Meeting, Anaheim, CA.
5. **Pettis, RJ**, Hickey, AJ (1996) Alveolar macrophage activation by muramyl dipeptide aerosols in guinea pigs: Effects on cellular morphology, poster, AAPS Southeast Regional Meeting, Research Triangle Park, NC.
6. **Pettis, RJ**, Hickey, AJ (1996) Effect of muramyl dipeptide aerosols on guinea pig alveolar macrophages, Pharm. Res., 13(9):S166.
7. **Pettis, RJ**, Knowles, MR, Olivier, KN, Hickey, AJ (1996) Ionic interaction of amiloride and uridine-5'-triphosphate (UTP) in solution, Pharm. Res., 13(9):S179.
8. **Pettis, RJ**, Sutter, D, Dekker, J, Bock, R (2000) Microfabricated microneedles for disruption of skin barrier function, poster, 2000 AAPS Annual Meeting and Exposition.
9. Mikszta, J, Alarcon, J, Brittingham, JM, Dekker, JP, **Pettis, RJ**, Harvey, N G Microdevice-Based Topical Delivery of DNA and Subunit Vaccines. AAPS PharmSci Vol. 2, No. 2, Abstract 2307 (2000)
10. **Pettis, RJ**, Haider, I, Mikszta, J, Alarcon, J, Brittingham, JM, Davison, N, Solbrig, C, Zahn, J (2001) Hollow microneedle drug delivery systems: Biomechanical characterization and vaccine delivery, AAPSPharmSci, Vol. 3, No. 3

11. Haider, I, **Pettis RJ**, Davison, N, Clarke, R and Zahn, JD (2001) Biomedical and Fluid Flow Characterization of Microneedle Based Drug Delivery Devices, American Society of Biomechanics, San Diego, CA
12. **Pettis, RJ**, Harvey, N, Sutter, D, McFarland, A, Pollack, G, Leipmann, D, Zahn, J (2002) Intradermal insulin delivery via MEMS fabricated microneedles, poster, 2002 AAPS Annual Meeting and Exposition,
13. **Pettis, RJ**, Kaestner, S, Sutter, D (2003) Microneedle delivery of GCSF leads to unique pharmacokinetic advantages, poster, 2003 AAPS Annual Meeting and Exposition, Salt Lake City, UH
14. **Pettis, RJ**, Kaestner, S, Sutter, D, Fentress, J, Harvey, N (2003) Microneedle-Based Intradermal Delivery of Insulin to Diabetic Swine: A Novel Parenteral Administration Method with Unique PK/PD Outcomes, podium, 2003 CRS Annual Meeting, Honolulu, HA
15. **Pettis, RJ**, Kaestner, S, Sutter, D, Fentress, J, Harvey, N (2004) *Microneedle-Based Intradermal Delivery of Insulin Enables Unique PK/PD Outcomes*, 2004 AAPS Annual Meeting, Baltimore, MD
16. Jiang, G, **Pettis, RJ**, Kuo, S, Harvey, AJ, Eicher, K, Kaestner, SA, Mitchell, M, Hwang, R, Haider, MI, Sullivan, V Intradermal delivery of novel sildenafil formulations, 2004 AAPS Annual Meeting, Baltimore, MD
17. Harvey, AJ, Kaestner, SA, Sutter, DE, Fentress, JK, **Pettis, RJ** (2005) Microneedle based delivery of follicle stimulating hormone : comparative pharmacokinetics vs. standard IM Therapy, 2005 CRS Annual Meeting and Exposition, Miami, FL
18. **Pettis, RJ**, Nycz, C, Harvey AJ, Karl K, Dunn B, Ramadan, S, Foster P (2006) In Vivo Cellular MRI for Tracking the Growth and Fate of Melanoma Cells Transplanted into Lymph Nodes of Mice 2006 Society for Molecular Imaging Meeting, Kona, HI
19. Sharma R, Kwon S, Houston, JP, Ke, S, Sevick, EM, Nycz, CM, Sutter, DE, **Pettis, RJ** (2006) Dynamic Lymph Node Mapping Using an Optical Imaging Agent Administered with a Novel Delivery Device 2006 Society for Molecular Imaging Meeting, Kona, HI
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23. Harvey, AJ, Kaestner, SA, Karl, K, Reed, C, **Pettis, RJ** (2007) Lymphatically Targeted IL-2 via Microneedle Based Intradermal Delivery Enhances Melanoma Therapy, 2007 AACR National Meeting, Los Angeles, CA
24. Harvey, AJ, Kaestner, SA, Karl, K, **Pettis, RJ** (2007) Lymphatic Targeting via Intradermal Delivery for Diagnostic and Therapeutic Applications, 2007 ISCMLS National Meeting, San Francisco, CA

Current or Completed NIH Research Support

None